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Metabolic Rewiring in Radiation Oncology Toward Improving the Therapeutic Ratio

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To meet the anabolic demands of the proliferative potential of tumor cells, malignant cells tend to rewire their metabolic pathways. Although different types of malignant cells share this phenomenon, there is a large intracellular variability how these metabolic patterns are altered. Fortunately, differences in metabolic patterns between normal tissue and malignant cells can be exploited to increase the therapeutic ratio. Modulation of cellular metabolism to improve treatment outcome is an emerging field proposing a variety of promising strategies in primary tumor and metastatic lesion treatment. These strategies, capable of either sensitizing or protecting tissues, target either tumor or normal tissue and are often focused on modulating of tissue oxygenation, hypoxia-inducible factor (HIF) stabilization, glucose metabolism, mitochondrial function and the redox balance. Several compounds or therapies are still in under (pre-)clinical development, while others are already used in clinical practice. Here, we describe different strategies from bench to bedside to optimize the therapeutic ratio through modulation of the cellular metabolism. This review gives an overview of the current state on development and the mechanism of action of modulators affecting cellular metabolism with the aim to improve the radiotherapy response on tumors or to protect the normal tissue and therefore contribute to an improved therapeutic ratio.

Keywords: radiation, radiotherapy, metabolism, cancer, oncology, drug repurposing

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INTRODUCTION

Cancer incidence is predicted to almost double, from 12.7 million in 2008 to 22.2 million cases in 2030 (1), resulting in a high burden on the healthcare system, but also necessitating the demand for efficient therapies. Although cancer survival rates are improved over the last decades, metastases contribute for the majority of cancer-related deaths (2). Approximately 50% of all cancer patients undergo radiotherapy during their treatment, either as monotherapy, but more frequently in combination with surgery, chemotherapy or immunotherapy, either to treat primary tumors and/or metastasis, or as a palliative treatment (3–11). Different therapies are commonly combined as it improves tumor control, progression-free survival and overall survival rates (12–16). Unfortunately, combination treatments approaches can potentially increase systemic toxicity. In order to overcome this problem, there is a need for a higher therapeutic selectively, which can be accomplished by enhancing tumor

treatment sensitivity while reducing adverse effects. This improved therapeutic ratio, is a favorable tradeoff between the tumor control and the radiation-induced toxicity (17).

One of the hallmarks of many cancer cells, namely the reprogramming of the cellular metabolism, has recently gained again the attention of researchers and clinicians. Rewiring the malignant metabolism is an interesting approach to considerably affect the radiotherapy response in order to enhance the therapeutic ratio (18, 19). This review gives an overview on the mechanisms and current status of potential radiosensitizers and protectors in relationship to rewire the cellular metabolism and thereby enhancing the therapeutic ratio (**Tables 1** and **2**).

METABOLIC REWIRING IN CANCER

Metabolic plasticity is crucial to ensure cellular survival since it enables the cell to adapt to changing nutrient demands and oxygen conditions. Therefore, metabolic adjustments are tightly regulated by extrinsic signals, such as growth factors, mediating the cell's response to changed environmental conditions. In contrast to healthy cells, the metabolism of primary cancer cells or metastatic lesions is, to a certain extent, uncoupled from external stimuli providing continuous resources for proliferation, growth, and metastatic niche formation (107–109). This is caused for instance by oncogene activation and/or loss of

TABLE 1 | Compounds with potentially radiosensitizing properties.

Compound	Mode of action	Specificities	References
HIF-1 signaling			
Deguelin, SH-14	Akt inhibition, downregulation HIF-1α, reduced hexokinase expression	Potential CI inhibitor- Development of Parkinson's disease-like syndrome in rat; SH-14 is a deguelin derivative	(20, 21)
Vandetanib	Inhibition, EGFR, HIF-1α signaling interference	FDA-approved for medullary thyroid cancer therapy	(22–27)
Berberine	Downregulation HIF-1α & VEGF		(28–31)
Rg3	Inhibition NF-κB, decreased expression HIF-1α & VEGF		(32, 33)
Cellular metabolism			
Glucose metabolism			
BAY-876	GLUT1 inhibition	*In vitro* cisplatin sensitizer, radiosensitizing effects unclear	(34, 35)
WZB117	GLUT1 inhibition		(36, 37)
2-DG, WP1122	Glucose analogue, hexokinase inhibition, radiosensitizing mechanism unclear	Tumor staging and metabolism profiling *via* PET-imaging using 2-DG coupled to positron-emitting isotopes; WP1122 is a 2-DG analogue	(38–41)
Lonidamine	Glycolysis inhibition, TCA cycle & CII interference	Negative results in clinics	(42–44)
Devimistat	Deregulation TCA cycle enzymes, ROS induction	In phase 2/3 trials combined with chemotherapeutics; No studies about combination with radiotherapy	(45, 46)
FH535 and Y3	Distortion mitochondrial membrane potential, apoptosis inducer	Y3 is an FH535-analogue	(47, 48)
Ivosidenib	$IDH1_{mut}$ inhibition	FDA-approved for acute/refractory AML	(49)
Enasidenib	$IDH2_{mut}$ inhibition	FDA-approved for acute/refractory AML	(50, 51)
Vorasidenib	$IDH1/2_{mut}$ inhibition	Clinical trials	(52, 53)
BAY-1436032	$IDH1_{mut}$ inhibition	Clinical trials	(54, 55)
Complex I			
Metformin	Inhibition CI, oxygen accumulation and subsequent HIF-1-α destabilization, reduces PI3K/Akt signaling	FDA-approved for anti-diabetes therapy	(56, 57)
Phenformin	CI inhibition	Redrawn, induces lactic acidosis in diabetes patients; Clinical trials phase I	(58, 59)
Papaverine	CI inhibition and PDE10A	FDA-approved as anti-vasospasm therapeutic*; In vivo* radiosensitization	(60, 61)
SMV-32	CI inhibition	Papaverine derivative*; In vivo* radiosensitizing; Clinical trials phase I	(61)
BAY 87 2243		*In vivo* radiosensitizing; Clinical trials status unclear	NCT01297530
IACS-010759		Radiosensitizing effect unclear	NCT03291938 NCT02882321
Complex III			
Atovaquone	Complex III inhibition	FDA-approved for anti-malaria therapy; Clinical trials phase I	(62, 63)
Pyrazinib	OCR/ECAR reduction	Precise target unknown	(64)
Other pathways			
ADI-PEG	Arginine depletion	Arginine deiminase and polyethylene glycol chimera- Clinical trials in combination with chemotherapy	(65–67)
Orlistat	FASN inhibition	FDA-approved for obesity-management	(68)
Fenofibrate	Activates PPARα, metabolic reprogramming *via* CPT1, AMPK and HK2 Prevention of HIF-1 stabilization	FDA-approved for hypercholesterolemia, mixed dyslipidemia and severe hypertriglyceridemia	(69–71)
Redox signaling			
Telaglenastat	GLS inhibition	Improved bioavailability, chemotherapeutic and immunotherapeutic outcomes FDA-approved for advanced renal cell carcinomas	(72–75)
Auranofin	TrX-reductase inhibition	FDA-approved for arthritis therapy	(41, 76)

The compounds are grouped according to their intracellular effects.

TABLE 2 | Compounds with potentially radioprotective properties.

Compound	Mode of action	Specificities	References
Radical scavengers			
Amifostine, PrC-210	ROS scavenger, accumulates in normal tissue, precise mechanism unknown	FDA approved for radioprotective effects PrC-210 is an amifostine analogue	(77–81)
MNSOD-PL	Mitochondrial localization		(82)
JP4-039	fusion peptide, Mitochondrial localization		(83, 84)
DSePA	ROS scavenger	Limited tumor uptake accumulation in lung and intestine	(85, 86)
Inflammation mitigators			
Celecoxib	COX2 inhibitor	Reduces skin toxicity, phase 2 clinical trial FDA-approved for rheumatoid arthritis	(87)
Vitamin E, γ-tocotrienol	Reduction in radiation-induced lipid peroxidation	Tumor radiosensitizing effects γ-tocotrienol is a Vitamin E derivative	(88, 89)
Ascorbic acid	Downregulation of MnSOD in tumors		(90, 91)
Curcumin	Blocks NF-κB signaling		(92)
Melatonin	NF-κB downregulation, depleting hydroxyl radicals,stimulation of SOD and GPx		(93–97)
CAPE	Suppression of NF-κB-signaling, ROS disbalance	Tumor radiosensitizing effects	(98, 99)
DNA repair			
RSV, HS-1793	Mcl-1 downregulation, cell cycle arrest, DNA repair	HS-1793 is an RSV analogue	(100–102)
Dietary Intervention			
STF	Differential stress response,	Phase I/II clinical trial	(103–105) NCT01754350
Ketogenic Diet	Differential stress response	Phase I/II clinical trial- Used in epilepsy treatment Clinical trials for cancer treatment ongoing	(106) NCT03451799 NCT02516501

The compounds are grouped according to their intracellular effects.

function in tumor suppressors. Consequently, malignant cells are depended on anabolic pathways and rewire their metabolism to meet their increasing demand for adenosine triphosphate (ATP), macromolecules and reactive oxygen species (ROS) scavengers due to their high proliferative potential (110). Metabolic patterns vary between cancer cells, depending on several intrinsic and extrinsic factors, such as the oncogene type and its microenvironment. The tumor microenvironment is often, in contrast to normal tissues, deprived from nutrients and oxygen due to a poor and imbalanced vascularization. Tumor cells therefore are capable to adapt their metabolic need by restructuring their metabolism and maintain a high biosynthetic potential by altering their carbon metabolism such as their intracellular glucose or glutamine pathways (111–113).

A prominent example for the rewiring of metabolic pathways in cancer cells is the "aerobe glycolysis," also named the Warburg effect. Aerobe glycolytic cells display an increased glucose uptake which they convert, in contrast to normal cells, into lactate instead of pyruvate in presence of oxygen (114–116). This seems quite paradoxal since oxidative phosphorylation (OXPHOS) remains possible as oxygen is available and has a higher ATP yield. However, tumor proliferation also depends on anabolic pathways derived from the glycolysis. A balanced exit of glycolytic intermediates ensures that the anabolic pathways are constantly replenished and (intermediate) products are transferred to the pentose-phosphate-pathway (PPP), fatty acid (FA) synthesis and tricarboxylic acid (TCA) cycle in order to meet tumor's metabolic need to proliferate. Glucose-6-phosphate is a central glycolytic intermediate as it can either be used by an irreversible oxidative arm and a reversible non-oxidative arm of which the oxidative arm contributes to reduced nicotinamide adenine dinucleotide phosphate (NADPH) production. The metabolic flux of the PPP is important to maintain a redox balance as reduced NADPH is a necessary cofactor for FA-synthesis and glutathione peroxidase (117, 118). The sufficient supply of anabolic pathways with intermediates is ensured by an altered regulation, for example the overexpression of the pyruvate kinase M2 (PKM2) in many tumors. This less efficient splice variant of the pyruvate kinase M1 catalyzes the conversion of phosphoenolpyruvate to pyruvate limiting the influx of pyruvate into the TCA cycle (119–121). Despite the higher fermentation rate, many cancers with an intact mitochondrial function still maintain their ATP pool using the Electron Transport Chain (ETC) and ATP-synthase (122). Due to the limited pyruvate production, alternative anaplerotic pathways are very important to sustain the TCA cycle, which recycles reduction equivalents that are crucial for the redox balance.

Next to glucose, also glutamine can refill the TCA cycle and maintain redox homeostasis. The glutamine pathway fuels the TCA cycle *via* glutamate and α-KG where oxaloacetate (OAA) gets converted into aspartate in order to support nucleotide synthesis (113). Vazquez et al. has given a comprehensive overview and graphical representation of the different substrates and connections between different oncological metabolic pathways (123). Extracellular glutamine is transported into the cells using transporters like SLC1A5. However, under nutritional stress conditions, tumor cells are also able to acquire glutamine by macromolecule breakdown within the cell (113). The uptake of those macromolecules by macropinocytosis can be stimulated by the oncogene *RAS* (113, 124). A large variety of oncogenes and tumor suppressors (e.g. *MYC, KRAS*, HIF-1α stabilization, *mTOR, P53, PTEN* etc.) have been found to influence the glutamine metabolism and its

effector pathways, emphasizing the importance of the glutamine pathway in tumor cell development, expansion and metastatic properties (113).

Cancers also often upregulate the *de novo* FA synthesis to provide enough lipids for membranes and other cellular structures (125). ATP-citrate lyase (ACT) is often upregulated to convert the TCA cycle derived citrate into acetyl-CoA. Consequently, a higher substrate influx into the FA synthesis occurs (126, 127). Lipid droplets are closely related to the fatty acids as they serve as storage depots of fatty acids. Lipid droplets can influence the metabolic regulation of tumor cells and tumor-associated immune cells. A relationship between lipid droplet accumulation, tumor establishment and aggressiveness has been demonstrated in different types of cancer, although this seems tissue type specific. In hypoxic tumor regions specifically, accumulation of lipid droplets has been observed, which is potentially related to an increased Fatty Acid Oxidation (FAO). The role of lipid droplets has been extensively reviewed before (128, 129). Inhibition of lipid droplet formation could potentially serve as a novel therapeutic target to be used in combination with therapies, such as radiotherapy, which modulate metabolism.

All these metabolic alterations are merely examples of metabolic rewiring to facilitate fast proliferation, growth and spread of cancer cells [extensively reviewed by (117, 130, 131)]. Importantly, the metabolic pattern varies between cancer cells and their tumor microenvironmental conditions. Interestingly, it has been suggested that cancer therapy itself, such as radiotherapy, can influence the cellular metabolism, which eventually will affect the cellular response to radiation (132–134). Therefore, a more profound understanding of these interactions is needed in order to enhance the therapeutic ratio.

RADIOTHERAPY AND METABOLISM

Radiotherapy is a fundamental treatment for most cancer patients since it enables the local control of many cancer types (3). Radiation results in deoxyribonucleic acid (DNA) double strand breaks (DSBs), single strand breaks (SSBs) and the radiolysis of water and other intracellular molecules, resulting in a ROS burst (135). This causes lipid peroxidation, protein oxidation and DNA damage, all processes massively harming cellular viability (136–141). Some lesions will remain unrepaired, resulting in genomic instability and cell death by mitotic catastrophe, even several mitotic divisions post radiotherapy. Cancer cells are more vulnerable to irradiation than normal cells since their DNA repair machinery is less efficient, making them more prone to genomic instability (142, 143).

Genotoxic effects of radiation are presumed to be caused by direct irradiation of the nucleus and not to the cytoplasm of cells, as direct irradiation of the nucleus is more lethal than the cytoplasmic dose (144). DNA repair is a highly energy demanding process in both tumor and normal tissue cells as interactions have been observed between mitochondrial ATP generation, DNA-repair and cell cycle kinase CDK1 (145, 146). Also, chromatin remodeling is an important mechanism involving DNA repair. Chromatin relaxation is highly ATP dependent and inhibition of glucose uptake can lead to energetic stress that will result to a decreased tumor survival upon radiation (147). DNA folding and remodeling involves acetylation of the DNA and donors for this acetyl-group are derived from acetyl coenzyme A (CoA), which is also required for the TCA cycle. Acetate-derived acetyl-CoA has also been linked to histone acetylation, suggesting that acetyl-CoA is an important substrate for gene regulation (148, 149). Limiting metabolic substrates will therefore have severe implications on the ability of cells to repair their radiation-induced DNA damage (150).

Nonetheless, the success of radiotherapy considerably depends on the therapeutic ratio since the radiation dose given to the tumor is limited by the maximal dose tolerated by the surrounding normal tissue. Both phenomena therefore contribute to the therapeutic ratio and are possible targets to increase radiotherapy efficacy. Radiosensitivity varies between cells, tissues and individuals and is determined by several intrinsic and extrinsic factors. Generally, hypoxia and cellular metabolism are two crucial determinants of cellular radiotherapy-response (151, 152). Hypoxic areas of the tumor can emerge from the immature tumor vascularization and the OXPHOS-dependent increased oxygen consumption rate (OCR), both due to the enhanced proliferative potential of cancer cells. Hypoxic areas reduce the cellular radiosensitivity since cells in hypoxic environments lack oxygen, the main component for ROS formation and inducing radiation-induced genotoxicity (153–155). Tumor survival and re-growth upon radiotherapy is also relying on the formation of new blood vessels. However, the mechanisms behind this new vessel formation are still a matter of debate and can be broadly categorized in: 1) the requirement of bone marrow–derived cells, or 2) the remaining viable endothelial cells form these new vessels (156–158).

Hypoxia regulates HIF signaling by promoting stabilization of HIF-1α, which can regulate target gene expression by binding to specific regulatory sequences in their promotor, the hypoxia response elements (HRE) (159). Hypoxia contributes to epithelial-mesenchymal transition (EMT) by binding to the HRE in TWIST (160, 161) and ZEB1 (162, 163), thereby supporting tumor invasiveness (164). Also, the downstream mechanisms of HIF-1α signaling influence cellular radioresistance by facilitating a metabolic switch, i.e. stimulation of glycolysis and OXPHOS downregulation, supporting the depletion of ROS and promoting angiogenesis (165–171). Importantly, HIF-1 expression is not only regulated by hypoxia, also the genetic background of tumors influences intracellular HIF-1 levels.

Tumor metabolism may also affect the radiation response since evidence suggests an enhanced radioresistance in cells harboring the Warburg phenotype. Studies observed an upregulation of glycolytic enzymes in Warburg-dependent cells, associated with elevated HIF-1 levels (172). Therefore, it is hypothesized that activated HIF-1 promotes the Warburg effect by e.g. activating glycolytic enzymes (173, 174). Genetic

interference with HIF-1–mediated effects on the glycolysis results in radiosensitivity (175, 176).

Metabolic Rewiring Upon Radiation of Tumors

Although malignant oncogene activation or loss of function of tumor suppressors alters the metabolism, radiation itself may also enhance metabolic alterations by influencing different signaling pathways. Among the several affected pathways, the PI3K/Akt and the NF-κB pathway play a crucial role in radiation-induced metabolic remodeling and the tissue response to radiotherapy (133, 134). PI3K/Akt are master regulators of glucose uptake. Normally, the PI3K/Akt pathway is activated by external stimuli, however, in many cancers PI3K and its downstream target Akt are constitutively activated due to mutations (177). PI3K can also be indirectly activated by radiation through stimulation of the PI3K upstream epidermal growth factor receptors (EGFR) (132, 178–180). Akt overactivation facilitates glucose uptake and intracellular accumulation of glucose by enhancing the glucose transporter expression and by activating hexokinase and phosphofructokinase 1, respectively. Furthermore, Akt stimulates FA synthesis by activating ATP-citrate lyase (133). These alterations may nurture malignant cells and thus, many radiosensitizers have been used to influence this pathway (181).

NF-κB is a family of five master transcription factors, influencing the expression of various genes, which is deregulated in many cancers with various effects depending on the cellular context. Radiation stimulates the pathway by enhancing the DNA binding affinity of NF-κB, its expression, the dissociation of the IκB complex and consequently its activation (182, 183). Thalidomide is a for multiple myeloma U.S. Food and Drug Administration (FDA) approved NF-κB modulator that interferes with the NF-κB activation and is currently investigated to reduce urinary complications, a normal tissue complication, upon irradiation of the pelvic region (184). As radiation activates NF-κB- and PI3K/Akt-signaling and thereby affects the radiation response modulation of those signaling pathways, thalidomide can contribute to enhance the therapeutic window (185, 186).

Next to radiation, also manganese superoxide dismutase (MnSOD or SOD2) is able to activate NF-κB and contributes as such to an aggressive tumor phenotype (187). MnSOD is a well-known and an important anti-oxidant enzyme located in the mitochondria and is required to scavenge super-oxides generated by the OXPHOS. Due to its function, MnSOD also acts as a tumor suppressor and reduced MnSOD has been shown to contribute to the oncogenic transformation of cells (188). However, elevated MnSOD activity has been reported to be involved in the increased invasion and metastatic potential of tumors (189). MnSOD also seems to play a role in rewiring the tumor's metabolism upon genotoxic conditions such as radiation exposure. CDK1 is found to contribute to mitochondrial energy production, which contributes to radiation induced DNA damage repair (145). MnSOD is able to interact with and activate these CDKs, and activated CDKs are involved in OXPHOS enhancement [reviewed by (190)]. This suggests that tumors are able to use the mitochondrial metabolism as a substitute metabolic system for glycolysis, when they are in a high metabolic need. Therefore, this phenomenon can contribute to growth, metastatic formation and a radiation resistance phenotype (190–192). Besides the signaling-pathway-mediated and radiation-induced metabolic shift of the tumor cells, also the metabolic rewiring of the TME and CSC population can play an important role in treatment response.

Metabolic Rewiring Upon Radiation of the Tumor Micro-Environment

As radio-, and/or chemotherapy exert untargeted effects, induced metabolic alterations are not exclusively restricted to the irradiated tumor cells, but also include tissues that are in close proximity to the irradiated tumor tissue, i.e. the tumor micro-environment (TME). This comprises different cell and tissue types, secreted factors, and proteins resulting in a complex ecosystem which is shaped to promote tumor survival and to establish a connection with the whole organism contributing to cancer stemness and metastasis. Here, the malignant metabolism plays a pivotal role as the increased oxygen and nutrient consumption, as well as the release of several (onco-) metabolites and other factors such as growth factors, cytokines and extracellular vesicles, into the TME establishes interactions with neighboring cells, in order to promote tumor growth and therapy resistance (193–195).

Cancer-Associated Fibroblasts

One of the components of the TME is the stroma. It is composed of different cell types such as fibroblasts, mesenchymal stem cells, endothelial cells, and lymphocytes. Cancer-associated fibroblasts (CAFs) are a prominent example how cancer cells metabolically modulate the TME to promote tumorigenesis and metastasis. In contrast to normal fibroblasts, CAFs are continuously active, secreting growth factors and cytokines to promote tumor growth. Moreover, the elevated ROS levels in cancer cells mediate metabolic reprogramming of CAFs towards glycolysis followed by an increased MCT4-mediated export of lactate in the TME. The enhanced lactate uptake of aerobic cancer cells by upregulated expression of the MCT1-lactate transporter fuels malignant metabolism (196). This tumor feeding through the TME is involved in tumor metastasis and therapy resistance as it decreases the tumor's dependency on proper vascularization, which is emphasized by the correlation of the tumor's CAF infiltration and prognosis (197–201). Radiation has been shown to activate CAFs and enhance their proliferative potential. Co-culture experiments with cancer cells have suggested that CAFs have a radioprotective effect on cancer cells through integrin-signaling, which stimulates the invasive potential of cancer cells (200, 202, 203).

Immune Cells and (Onco-)Metabolites

Furthermore, tumors can influence, due to their altered metabolism, the TME to establish an immune suppressive environment. This is important as the TME comprises a variety of immune cells, including tumor-suppressing cells like

natural killer (NK) cells, CD4/8$^+$ T-cells, proinflammatory M1 macrophages, dendritic cells and tumor-promoting immune cells *e.g.*, Foxp3$^+$ regulatory T-cells (Tregs), tumor-associated macrophages and myeloid-derived suppressor cells (MDSCs). The high anabolic rate of tumors results in hypoxic and nutrient-poor areas, which influence immune cell types massively as their function is determined by their metabolic program (204, 205). Glucose-deprivation results in T-cell and macrophage exhaustion as these cells depend on glycolysis to cover their demand for metabolic intermediates and energy (206). Moreover, the TME is a selective pressure for tumor-promoting immune cell types. Naïve T-cells favor the differentiation into Treg cells rather than into T-helper cells in a glucose and glutamine deficient TME as Tregs mainly rely on OXPHOS and FAO to meet their energy demand (207–209). The enhanced production of kynurenine caused by the expression of the tryptophan catabolizing IDO1 enzyme in cancer cells, cancer-derived vesicles and several other immune and stroma cells in the TME has immunosuppressing effects and is a predictor for poor prognosis in different cancer types. IDO1 stimulates the Treg-dependent recruitment and activation of MDSCs and the differentiation of CD4$^+$ to Tregs (210–214). Concomitantly, IDO1 inhibits tumor-antagonists like CD8$^+$ T-cells and NK cells (215, 216).

Radiation of the TME however provokes ambiguous responses, which is likely due to the heterogeneity in TME composition and the radiotherapy dosage (217). For example, radiation can exert immunosuppressive effects by decreasing the relative abundance of immunoreactive lymphocytes due to their inert higher radiosensitivity compared to immunosuppressive cells like MDSCs and Tregs (218–221). MDSCs exert immunosuppressive functions, amongst others, by depleting amino acids such as cysteine and arginine from the TME which impairs the function and activity of T-cells (222–224). Studies with high-dose or hypofractionated radiotherapy suggest that radiation potentially triggers an anti-tumor immune response. The release of cytokines, damage associated molecular patterns, tumor associated antigens and other factors by dying cells upon radiation activates CD8$^+$ T-cells, although this seems to be dependent on radiation-induced conventional DC1 activation which mediates the cross-priming of CD8$^+$ T-cells in the lymph nodes (225–228). The treatment with adjuvants rescued the absence of an improved radiation response in tumors with no DC1 activation. These observed differences may be due to the TME as for instance cancer cells are proposed to reduce the activity and functionality of DCs by inducing a Msr-mediated lipid uptake, which results in lipid accumulation and decreased antigen presentation (229, 230).

Another mechanism of tumors to interact with neighboring cells is the secretion of (onco-)metabolites from the TME, which are associated with tumor-promoting effects (231). The release of lactate, the end product of glycolysis, is promoted through hypoxia-mediated HIF-1 stabilization which results in the enhanced expression of monocarboxylate transporter 4 (MCT4). This leads to an increased acidification of the TME. Lactate exerts tumor-protecting effects by its inhibitory effects on T-cells, dendritic cells, natural killer cells, and tumor-associated macrophages (232–235) and its contribution to the induction of CD4$^+$ Treg cells (234). Tumors with loss or gain of function mutations in genes encoding TCA cycle enzymes such as succinate dehydrogenase (SDH) and isocitrate dehydrogenase (IDH) respectively, exhibit an accumulation of the oncometabolites succinate or 2-hydroxyglutarate (2-HG). Both promote tumorigenesis and metastasis formation by epigenetically initiating EMT as inhibitors of a-KG dependent dioxygenases and by their release into the TME (236). Succinate induces macrophage polarization into M2-like tumor-associated macrophages *via* succinate receptor activation and the PI3K-HIF-1α axis promoting metastasis (237). 2-HG is released by IDH-negative cancer cells and is proposed to affect T-cells as IDH-negative tumors display a significantly lower T-cell infiltration compared to IDH-wildtype tumors (238, 239). 2-HG uptake induces HIF-1α destabilization and a shift towards OXPHOS in T-cells which is associated with lower levels of T-helper cells and a higher Treg abundance (217). In mice, CD4$^+$ T cells display a decreased secretion of cytokines under hypoxia and 2-HG treatment (240). This exemplifies how the tumor metabolism participates in the shaping of its protective niche and how this reduces its radiotherapy response.

TME Involvement in Metabolic Rewiring of Cancer Stem Cells

The dynamic TME leads, amongst others, to a high heterogeneity of metabolic profiles within tumors (241). Particularly, differences between normal cancer and cancer stem cell populations need to be considered for efficient therapeutic interventions as cancer stem cells (CSCs) drive cancer progression and recurrence. Mostly, glycolysis-dependent CSCs have been observed but there are also reports about mitochondrial driven CSCs, which is likely to depend on the genetic background, TME and the proliferative capacity (242–248). CSCs seem to be metabolically flexible, switching from OXPHOS to glycolysis or vice versa upon inhibition of one of these pathways (248). Moreover, evidence suggests that the metabolic profile between normal cancer cells and CSCs varies so that effective therapies and relapse prevention potentially requires the interference with different pathways (248–251). Highly aggressive cancers such as triple negative breast cancer or glioblastoma are suggested to exhibit CSC populations and to mainly rely on a mitochondrial energy metabolism (251–254). Therefore, it may be necessary to combine mitochondrial and glycolysis metabolism inhibition, in order reduce the potential radioresistance and have a successful treatment.

IMPROVING RADIOTHERAPY RESPONSE BY TUMOR SENSITIZATION

Radiosensitizers aim to improve local tumor control and curation by enhancing radiotherapy-induced mitotic catastrophe of tumor cells without affecting normal cells.

Different strategies to enhance radiosensitivity have been explored, such as 1) the physical amplification of the irradiation intensity e.g. by nanoparticles (255), 2) interventions to selectively enhance the radiation-induced ROS production for instance by increasing intracellular oxygen levels (175) and 3) suppression of survival pathways such as ROS degradation pathways or DNA repair pathways (175, 256). As metabolism and radiation response are linked, modulation of the cellular metabolism is another promising strategy to increase tumor's radiosensitivity (**Figure 1**; **Table 1**).

Modulation of HIF-1 Signaling

Mutations in the TCA cycle enzymes IDH, SDH and fumarate hydratase (FH) lead to HIF-1 accumulation (257–259). Tumors with mutations causing SDH or FH deficiency exhibit TCA cycle disruption and a disbalanced redox status caused by a disrupted NADPH-recycling. Due to these mutations levels of succinate and fumarate augment and thereby influence cellular metabolism also through phosphorylation-mediated downregulation of pyruvate dehydrogenase (260). Next to hypoxia, also mutations in SDH, FH and IDH are involved in EMT of cells and contribute to the formation of metastasis. Furthermore, these enzymes enhance the metabolic shift towards glycolysis, as they also inhibit prolyl hydroxylases leading to stabilization of HIF-1 (261, 262). Therefore, compounds interfering with HIF-1 signaling might enhance radiosensitivity.

The radiosensitizer deguelin is a rotenoid naturally produced by *Leguminosae* and has been proposed to augment the tumor chemo- and radiotherapy response (263). It targets multiple signaling pathways including STAT3, c-myc and E-cadherin to de-regulate proliferation, angiogenesis and metastasis capability. Furthermore, deguelin facilitates apoptosis by promoting cell cycle arrest and Akt inhibition (20, 264, 265). Inactivation of Akt destabilized the anti-apoptosis factors XIAP, Mcl-1, and survivin, downregulated HIF-1 signaling and reduced hexokinase expression. The deguelin-caused Akt dysregulation has been shown to radiosensitize breast cancer cells, associated with increased G_2/M- arrest and caspase-dependent apoptosis (263). The mechanism of selective apoptosis induction of deguelin is unclear, but supposedly different caspase levels in normal and cancer cells influence the selectivity of deguelin (266). The use of deguelin is currently limited due to its assumed function as OXPHOS Complex I (CI) inhibitor (267). Caboni et al. demonstrated that rats receiving subcutaneous deguelin doses developed Parkinson's disease-like syndrome (267). *In vitro* results suggested similar molecular effects of the deguelin

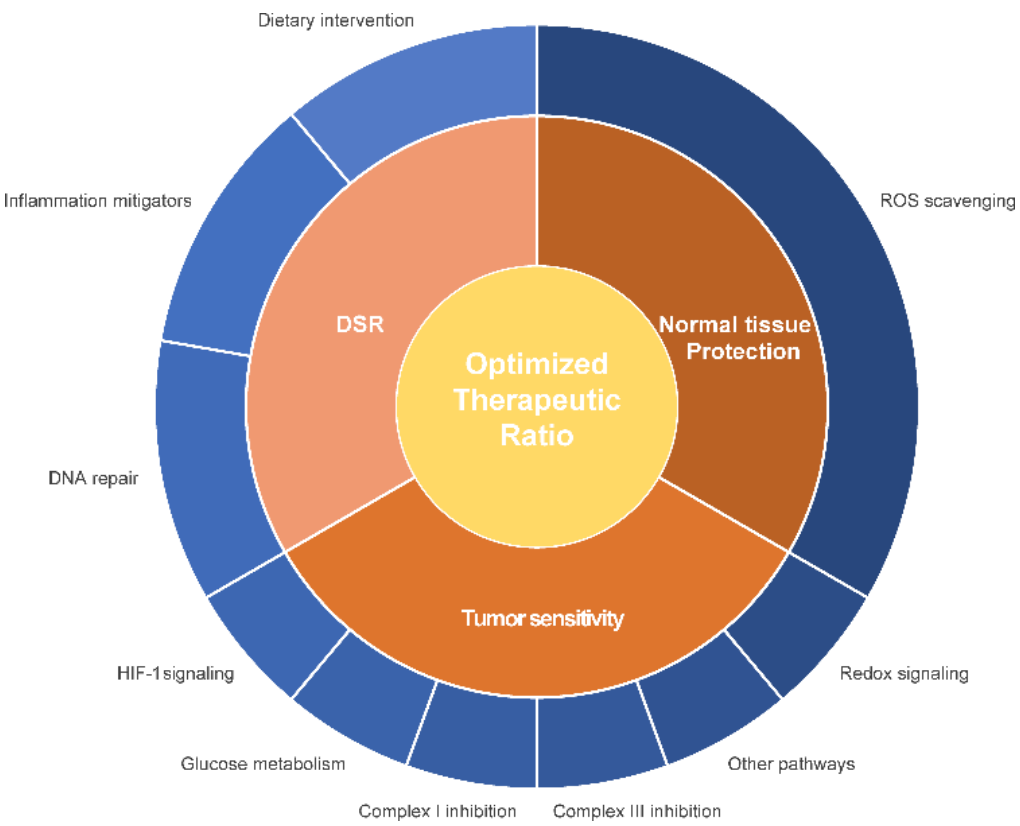

FIGURE 1 | Schematic representation of different interventions to improve the therapeutic ratio. Interventions can either improve the radiosensitivity of the primary tumor or metastatic lesion or protect the healthy tissue. Influencing the differential stress response between tumor and normal healthy tissue can contribute to an enhanced therapeutic ratio. Different pathways and proteins can be influenced in relationship to enhancement of the therapeutic ratio, such as mitochondrial and glucose metabolism, ROS scavenging and redox signaling, hypoxia response, DNA repair capacity and inflammation.

derivative SH-14 but less toxicity and higher solubility which potentially could be an alternative (21).

Vandetanib, a FDA-approved medullary thyroid cancer therapy that inhibits EGFR (22), impairs the HIF-1 pathway by targeting the mTOR–HIF-1α–VEGF signaling axis in breast cancer cells (23) and increases survival in advanced medullary thyroid carcinoma (268). Vandetanib is able to radiosensitize and improve overall survival in xenografts (24). Phase I clinical trials proved Vandetanib's safety in a (chemo)radiotherapy regimen for head and neck cancers (25) and brain metastasis of melanomas, although without differences for progression free survival (PFS) or overall survival (OS) (26). Additionally, adult SDH_{mut} gastrointestinal stromal tumor patients displayed treatment-related toxicities without partial or complete responses (27). The alkaloid Berberine also downregulated HIF-1-α and its downstream target vascular endothelial growth factor (VEGF) and reduced tumor invasiveness resulting in an improved radiotherapy response (28, 29, 269). Furthermore, berberine treatment results in decreased levels of RAD51, part of the homologous recombination mediated repair of irradiation-induced DSBs (30, 270) and induces a dose-dependent cell cycle arrest (31). Similarly, succinate and fumarate can, as both are competitive inhibitors of α-KG-dependent dioxygenases which control chromatin-methylation status (e.g. histone- and DNA-demethylases) (271), influence gene expression and DNA-repair mechanisms; such as hypermethylation of the O6-methylguanine-DNA methyltransferase promoter (272–274). Also, ginsenoside Rg3, a ginseng extract, modulates HIF-1α stabilization, VEGF expression and NF-κB activation upon hypoxia exposure and sensitizes tumor cell lines and xenograft to radiation (32, 33).

Altering Cellular Metabolism

The metabolism of malignant cells, especially pathways which are involved in the utilization of carbon as these are crucial for maintenance of cancer cell survival and proliferation, can be targeted directly. Prominent targets are the glucose metabolism, mitochondrial metabolism and antioxidant metabolism.

Glucose Metabolism Targeting

Glucose has a central function in the cellular metabolism and therefore several compounds have been developed which target the glucose import to reduce the glycolytic rate. BAY-876 is a highly selective small molecule inhibitor of the glucose transporter 1 (GLUT1), upregulated in many tumor cells and predictive for poor survival (34, 275–277). Moreover, BAY-876 demonstrated sensitizing effects towards cisplatin treatment in esophageal cancer cell lines (35). Its usefulness as a radiosensitizer needs to be investigated. WZB117, another promising GLUT1 inhibitor, re-sensitizes therapy-resistant breast cancer cells to radiotherapy and demonstrates anti-cancer effects in glioblastoma cells (36, 37).

The glucose analogue 2-deoxyglucose (2-DG) influences the radiotherapy response of cancer cells by interfering with glycolysis (38–40). Glucose and 2-DG compete for GLUT-mediated transmembrane transport. Both molecules are phosphorylated by hexokinase (HK) followed by phosphoglucose isomerase dependent metabolism, only possible for glucose. 2-DG, however, is not sensitive for the enzyme resulting in its accumulation and inhibition of HK. 2-DG mediated downregulation of glycolysis therefore reduces cell growth and proliferation of radioresistant cells (41) and reduces angiogenesis and invasiveness of tumor cells (278). However, the mechanism of 2-DG-mediated cellular radiosensitivity remains to be elucidated. Studies proposed that 2-DG reversed the radiation-induced cell cycle arrest which may contribute to later occurring cell death by mitotic catastrophe (38). Additionally, 2-DG-mediated disbalance of the cellular redox balance seems to promote radiation-induced cell death. Concurrent radiotherapy and 2-DG treatment led to 50% reduction of GSH levels while thiol-antioxidants reversed the 2-DG-induced radiosensitizing effects (39). Rashmi et al. showed that co-treatment with GSH (buthionine sulphoximine) and thioredoxin synthesis (auranofin) inhibitors enhanced the radiosensitizing effects of 2-DG *via* adenosine monophosphate-activated protein kinase (AMPK) stimulation and subsequently autophagic cell death (41).

Treatment with MLN4924, a SCF E3 ligase inhibitor, synergized with 2-DG and radiotherapy in breast cancer cells (279). On the other hand, combination of 2-DG with radioimmunotherapy has antagonistic effects and indicated that the treatment effect may rely on glucose availability and level of hypoxia (280). WP1122 is an analogue of 2-DG having an extended half-life and good oral bioavailability resulting into two-fold higher plasma concentrations compared to 2-DG and is capable of passing the blood-brain barrier. However, its effect on radiosensitivity remain to be elucidated (281).

Lonidamine 1-(2,4-dichlorobenzyl)-1H-indazole-3-carboxylic acid interferes with cellular metabolism in a very diverse manner. It can inhibit glycolysis *via* interference with hexokinase, contributing to intracellular lactate accumulation. Lonidamine also inhibits malate and fumarate formation in the citric acid cycle and it influences the ETC function by disturbing the mitochondrial transmembrane potential through inhibition of Complex II (CII) and the pentose phosphate pathway causing a decreased NADPH and glutathione pool (42, 282). Clinical studies in Head and Neck cancer showed improved survival rates (283). However, a prospective clinical trial for unresectable non-small-cell lung carcinoma (NSCLC) was negative for lonidamine in combination with radiotherapy versus radiotherapy alone (284). The lack of radiosensitization may be explained by the wide range of metabolic profiles observed in NSCLC (42, 43), although also the shift to the mitochondrial respiration due to potential tumor metabolic flexibility could be a potential explanation (285, 286). Also, lonidamine did not show any clinical effects in a large randomized trial in combination with chemotherapy (NCT00237536) (44).

Mitochondrial Metabolism Targeting

Beyond targeting glycolysis, the selective disruption of the mitochondrial metabolism might be another interesting approach. Devimistat (CPI-613), which recently received FDA fast-track designation for metastatic pancreatic cancer (NCT03504423), is a lipoate-analogue which dysregulates the

TCA cycle through inhibition of the pyruvate dehydrogenase (PDH) and ROS induced inhibition of ketoglutarate dehydrogenase (KGDH) (45, 287). CPI-613 also activates AMPK signaling *via* stimulated ROS production (e.g. at KGDH), resulting in deactivation of acetyl-carboxylase and FA-synthesis (288). Combination of CPI-613 with PDK1 activators led to a reduced mitochondrial membrane potential and stimulated mitochondrial autophagy (289). Demonstrating tolerable side effects, CPI-613 is now under investigation in combination with different chemotherapeutics in phase 2/3 trials, but its effect in combination with radiotherapy is yet to be examined (46, 290, 291). Similarly, FH535, and its analogue Y3, disrupts the mitochondrial membrane potential which results in a decreased ATP production, induces apoptosis and reduces migration and invasiveness. FH535 has shown promising results *in vitro* and *in vivo* for different tumor types however, to date no clinical studies are available (47, 48, 292–295).

Also, IDH has been investigated as target for metabolic interventions, as it is frequently mutated in many aggressive cancers such as gliomas and AML (296, 297). Next to TCA cycle and redox-balance disruption, gain of function IDH mutations result in the production of the oncometabolite (D)-2-HG, which inhibits α-KG-dependent dioxygenases and thus, influencing the gene expression of metabolism regulators such as TP53-induced glycolysis and apoptosis regulator (TIGAR) (298). TIGAR regulates the cellular NADPH levels by controlling PPP supply with the glycolytic glucose-6-phosphate, which is required for the production of ROS scavengers as reviewed by Trachootham et al. (299). Cells with low TIGAR levels are proposed to be more susceptible to radiation, as ROS scavenging could be influenced (298, 300). Furthermore, reduced DNA repair was observed in presence of IDH_{mut}, though inhibition of $IDH1/2_{mut}$ did neither alter the radiation sensitivity nor radiation resistance of chondrosarcoma cell lines (298, 301). Comparing the treatment response between IDH_{wt} and IDH_{mut} AML and glioma patients upon salvage and chemoradiotherapy suggested an IDH mutation status independent treatment response (302, 303). However, targeting these variants specifically also has shown promising results. Ivosidenib and Enasidenib (AG-221) inhibit $IDH1_{mut}$ and $IDH2_{mut}$ respectively and are both FDA approved for treatment of acute or refractory AML (49, 50) and reduce invasiveness (109). Especially patients, who are not eligible for cytotoxic treatments, can benefit (51). However, adaptive IDH mutations can result in resistance to Enasidenib and Ivosidenib, causing a decrease in glioma treatment efficacy (52, 304). Therefore, other IDH inhibitors are under development. Vorasidenib has been shown to be a good candidate for glioma treatment as it passes the blood-brain-barrier (52, 305). Its safety and efficacy is currently investigated in multiple clinical trials (53, 306). Furthermore, the $IDH1_{mut}$ inhibitor BAY-1436032 delays xenograft growth (54) and has also entered clinical trials (55, 307).

Also, inhibitors of different OXPHOS complexes are capable to enhance radiation response, this related to improved tumor reoxygenation. As they increase intracellular oxygen availability due to inhibition of OXPHOS, a decreased oxygen consumption may result in higher oxygen levels eventually re-sensitizing tumors to radiotherapy (308). Consequently, many OXPHOS inhibitors are tested for their potential radiosensitizing effects of tumors.

Complex I Inhibitors

The two CI (NADH:ubiquinone oxidoreductase) inhibitors metformin and papaverine are FDA-approved for non-cancerous diseases and are currently investigated for their radiosensitizing properties. Metformin is an anti-diabetic treatment and has already shown anti-cancer efficacy (309) and the potential to reduce metastatic potential (310, 311). Metformin was described to target the IGF receptor and consequently, indirectly mediates the downregulation of PI3K/Akt signaling (56, 312, 313). Additionally, metformin inhibits CI of the ETC resulting in a reduced ATP/AMP ratio (56, 313) and stimulates AMPK to promote cell cycle arrest and autophagy (314, 315). While impairing OXPHOS function, metformin administration results in oxygen accumulation and subsequently destabilization of (HIF-1-α) (316–318) and favors the formation of ROS after irradiation (319). Several *in vitro* studies suggested that metformin enhances the radiosensitivity of cancer cells. Zannella et al. demonstrated that metformin treatment prior to radiotherapy increased the intra-tumor oxygen levels in colorectal carcinoma xenografts, which enhanced the radiotherapy response (320). In contrast, De Bruycker et al. stated an anti-hypoxic effect of metformin in colorectal cancer xenografts, but a metformin-mediated enhanced radiotherapy response was not observed (321). These contradicting reports about metformin's radiosensitizing effects may be caused by different experimental conditions since it is suggested that metformin only exerts its radiosensitizing effects in p53 mutated genetic contexts (322). Indeed, differences in mutations between HCT116 and Colo205 corroborate these findings (320, 321).

Completed Phase I trials of metformin combined with radiochemotherapy in head and neck squamous cell carcinoma patients are promising with a two years OS of 90%, a PFS of 84% and manageable toxicity, compared to historical control rates of 80% (OS) and 65% (PFS), although only a small cohort was included (57). Currently, metformin is investigated in several phase II trials in combination with different treatments (NCT02945813, NCT04275713, NCT02186847). Metformin's tissue-specific uptake depends on the expression of organic cation transporter 1 (OCT1) transporters, explaining its low bioavailability (58, 323). The related biguanide, but more lipophilic, phenformin is suggested to have a higher bioavailability, does not rely on OCT1 expression for uptake and has a similar effect on cellular metabolism as metformin (58, 324, 325). However, it has been redrawn from the marked in the 1970s as it causes lactic acidosis in diabetic patients (326). Nevertheless, it may be a promising anti-cancer drug since it re-sensitizes resistant cells to chemo- and radiotherapy (327, 328) and synergizes with chemotherapeutics allowing a lower dosage of chemotherapeutics (329). Its safety as an anti-cancer drug is currently being investigated in phase I trials (59).

Papaverine (PPV) inhibits phosphodiesterase 10A (PDE10A) and is an FDA-approved vasospasm treatment (60). As it also targets CI of the ETC, it might exhibit anti-tumor properties. PPV sensitizes cells and xenografts to radiation, explained by a decreased OCR (61). The PPV derivative SMV-32 has been developed as a specific CI inhibitor, without affecting PDE10A activity. Its administration results in decreased tumor hypoxia leading to an improved radiotherapy response with acceptable toxicity profile in xenografts (61). Currently, the safety and tolerability of SMV-32 is assessed in a Phase I trial (NCT03824327).

Next to metformin and PPV, the small molecule CI inhibitors BAY 87-2243 and IACS-010759 presented anti-cancer effects *in vitro* and *in vivo* (330–332). BAY 87-2243 exhibited radiosensitizing effects in xenografts and is suggested to synergize with serine-threonine kinase inhibitors in $BRAF_{mut}$ xenografts (333, 334). A phase 1 study with BAY 87-2243 was initiated in 2011 but terminated with an unclear status (NCT01297530). IACS-010759 has entered phase 1 trials investigating its safety and tolerability in solid tumors, lymphoma and leukemia (NCT03291938, NCT02882321). However, its treatment sensitizing effects remains to be elucidated.

Complex III Inhibitors

Atovaquone (ATO) inhibits Complex III (CIII) of the ETC and is FDA-approved as an anti-malaria treatment. In xenografts, radiotherapy combined with ATO delays tumor growth, which has been associated with reduced hypoxia. ATO-treated xenografts display a significant higher reduction in OCR as compared to metformin treatment (73.7% vs 43.1%). Additionally, ATO targeted the pyrimidine synthesis enzyme dihydroorotate dehydrogenase (DHODH) (62). It is assumed that ATO mainly exerts its radiosensitizing effects *via* CIII inhibition since the potency against DHODH was markedly lower (335–337). The results of a first phase 1 study investigating the anti-hypoxic effects of ATO in NSCLC patients are yet to be published (63). Hypoxia mitigating effects of inhibitors of the ETC complexes II, IV and V are also investigated (338–346).

The small molecule inhibitor pyrazinib (P3) reduces OCR and extracellular acidification rate (ECAR) in zebrafish and is associated with an improved radiosensitivity in esophageal cancer cell lines, although the precise mechanism remains to be elucidated. Buckley at al. hypothesized that the P3 target lies upstream of glycolysis and OXPHOS. Furthermore, they suggested that P3 acts as a radiosensitizer under hypoxic conditions (64).

Other Metabolic Pathways

Modulation of the arginine metabolism is suggested to increase the cellular sensitivity to anti-cancer therapies. ADI-PEG 20, a chimera of the arginine deiminase (ADI) and polyethylene glycol (PEG) (347), consumes the cellular arginine by catalyzing the conversion of arginine to citrulline, a clinical marker for radiation-induced tissue toxicity (348). Moreover, ASS1-deficient pancreatic cancer cells displayed enhanced radiosensitivity through arginine depletion after ADI-PEG 20 treatment (65).

Arginino succinate synthetase (ASS1) produces endogenous arginine from citrulline, however, many cancer cells exhibit arginine auxotrophy e.g., due to ASS1 deficiency (349–351). Being the precursor for various molecules including pyrimidines, cells display an enhanced vulnerability in arginine-depleted environments (352, 353). ASS1-deficient cancer cells show synthetic lethality and an inhibited Warburg phenotype under arginine depletion (66). Phase 1 trials in combination with chemotherapeutics in different cancer types reveal tolerable side effects and hint towards a treatment response (354, 355). Interestingly the response depends on the ASS1 status (67, 356). Currently, phase 2 trials investigate the combination of different chemotherapeutics in several cancer types including pleural mesothelioma and hepatocarcinoma [NCT02102022, NCT02709512 (357, 358)].

Manipulation of the FA metabolism can increase the efficacy of chemotherapy and radiotherapy. Different compounds modulating FA metabolism have been investigated for their potential applications in cancer treatment by either improving therapeutic responses, reducing tumor progression or metastatic formation. The FDA-approved obesity therapeutic agent orlistat inhibits FA synthase blocking a crucial anabolic pathway (68) and is associated with an enhanced response to chemotherapeutic treatments and radiotherapy and experimental reduced metastasis formation (359–361). Fenofibrate (FEN), a PPARα agonist, reverses metabolic reprogramming of cancer cells leading to enhanced radiosensitivity *in vitro* and *in vivo* under hypoxic conditions (69, 70) and also reduces metastasis formation of melanomas (362). FEN activates AMPK signaling and FA oxidation *via* carnitine palmitoyltransferase 1 (CPT1) and inhibits PI3K/Akt signaling resulting in reduced hexokinase 2 levels and glycolysis (71). FEN also prevents HIF-1 stabilization (69, 70) and the disruption of the HIF-1α/VEGF axis may contribute, when combined with radiotherapy, to G_2/M-phase arrest (70, 363).

Influencing Redox Signaling in Tumors

The indirect ROS-mediated DNA damage is believed to be a main factor to activate cell death pathways upon radiotherapy (364, 365). Since proliferating cells have a naturally higher ROS production, cancer cells need to compensate this by simultaneously increasing the production of protective antioxidants (366). Hence, the impairment of anti-oxidants increases the radiotherapy effect (367). Moreover, excessive ROS levels induced by mutations and/or radiotherapy are suggested to induce ferroptosis, a phenomenon describing the Fe^{2+}-dependent cell death induced by high levels of peroxidized lipids (368). Radiotherapy induced ferroptosis by further enhancing ROS formation and activating long-chain-fatty-acid CoA ligase 4 (ASCL4) to promote the formation of polyunsaturated fatty acid phospholipids (PUFA-PL) (368). Contrary, Lei et al. has described reduced ferroptosis upon irradiation, depending on the genetic background through induction of glutathione peroxidase (GPX) and SCL7A11 (part of X_c-antiporter), which increased the reduction equivalent pool (368). Others however reported that radiotherapy suppresses

SLC7A11 expression indirectly *via* ATM downregulation and thus limits the import of cysteine, a GSH precursor (369). Therefore, manipulation of this pathway is associated with radiation sensitivity. Firstly, it is stated that the inhibition of X_c or GPX induces ferroptosis and sensitizes cell lines and xenografts to radiotherapy due to a lack of glutathione (GSH) (369–371). Second, many neoplasms increase their glutaminolysis e.g., by oncogene (*myc*)-driven glutaminase (GLS) overexpression.

GLS produces the GSH precursor glutamate and its inhibition resulted in tumor growth delay (252). Although several GLS inhibitors synergize with anti-cancer treatments (72, 372, 373), their application in clinical practice is often limited due to its low bioavailability (374). Telaglenastat (CB-839) demonstrates improved bioavailability and synergizes in xenografts with radio- and chemotherapy (72, 73). In clinical trials combined with chemo- and immunotherapeutics it has demonstrated promising results with tolerable side effects (74, 75, 375, 376). Thirdly, supplementation of PUFAs pre-, during or post radiotherapy demonstrates synergism in rat astrocytoma cells and xenografts (377–379) as a result of COX2 downregulation and reduced vascularization (379).

Moreover, inhibitors of enzymes maintaining the redox balance, such as thioredoxin reductase (TrXR), are considered potential targets. Auranofin is a TrXR inhibitor already implemented as arthritis therapy. Its administration sensitized cancer cells to radiation preventing ROS degradation (76).

PROTECTING NORMAL TISSUE DURING RADIOTHERAPY

Radiotherapy cannot always be applied in curative doses as damage in the adjacent normal tissues is dose limiting. Additionally, the bystander effect, i.e. the phenomenon that irradiated cells negatively influence non-irradiated cells, also limits radiotherapy efficacy (380). Normal tissue cellular damage affects quality of life post radiotherapy tremendously. Therefore, it is crucial to identify strategies to protect normal tissues without reducing the efficacy of radiotherapy. Interventions aim to selectively augment the normal tissue cellular survival pathways, e.g., ROS depletion and DNA repair pathways counteracting the radiation-induced ROS burst and DNA lesions (**Figure 1**). The differential metabolic pattern between malignant and healthy cells represents a suitable target to modulate these pathways selectively within normal tissues. The NF-κB signaling pathway plays a pivotal role in the response of tissues to radiation. Its activation results in stimulation of inflammatory and apoptosis pathways in normal tissues, promoting tissue damage and cell death and therefore limits the applied radiotherapy dose (381). Consequently, many interventions aim to modulate NF-κB signaling counteracting the unwanted side effects. Here, we focus on radioprotectors influencing the metabolic pathways attenuating radiotherapy-induced effects in normal tissues. These can be broadly classified based on their effect into radical scavengers, inflammation mitigators and DNA repair modulators (**Table 2**).

Radical Scavengers

The IR-induced ROS burst diminishes levels of endogenous ROS scavengers which has to be recycled. Therefore, agents that chemically reduce ROS or activate pathways/molecules facilitating ROS depletion selectively in normal cells can ameliorate radiation-induced damage (**Figure 1**).

Amifostine, a ROS scavenger, is FDA-approved for its radioprotective effects in ovarian and head and neck cancer patients. It is activated *via* dephosphorylation by alkaline phosphatases, which are highly expressed on the surface of normal cells; thus, amifostine accumulates preferentially in normal tissues (77, 382). The precise mechanism of action is unknown, but several have been proposed. Firstly, its active form harbors free thiol groups to reduce intracellular ROS-induced damage and to prevent delayed genomic instability in cells (383, 384). Second, amifostine reduces oxygen consumption and induces HIF-1, which correlated with its radioprotective effect. Koukourakis et al. argued that this oxygen-depletion may result from the reaction between oxygen and the free thiol, which leads to hypoxia for a short time, inducing HIF-1. However, the precise mechanism of amifostine-induced HIF-1 stabilization is unclear (385). Thirdly, its administration was associated with DNA condensation reducing damage efficiency (386). Fourthly, amifostine may alter lipid membrane dynamics affecting membrane proteins and therefore it can influence downstream signaling pathways of transmembrane receptors (387).

The results of clinical trials using amifostine are ambiguous, some describing radioprotective effects whereas some did not observe any effect (388). Prostate cancer patients receiving radiotherapy combined with amifostine produced significant improvements in acute and late bowel quality of life (up to 1 year after therapy), measured using the Expanded Prostate Cancer Index Composite (EPIC) score. Differences between dose groups are evident from week 7 onwards. The RTOG gastrointestinal (GI) toxicity score mirrored these results stating a lower GI toxicity in probands receiving a higher amifostine dose, although in a non-significant manner (78). Dose-related adverse effects induced by amifostine include nausea and hypotension and seems to be affected by the route of administration. Bardet et al. compared daily intravenous (iv) with subcutaneous (sc) administration of amifostine prior to radiotherapy and reported higher occurrence of hypertension upon iv injection, while a higher number of patients suffering from xerostomia upon sc administration (79). Another study observed lower rectal mucositis after intrarectal amifostine administration before radiotherapy, while sc application resulted in a lower urinary toxicity (389). Aminothiol analogues of amifostine, such as PrC-210, demonstrate less adverse effects in rodents and significantly prolongs the survival of $P53^{-/-}$ mice upon irradiation (80, 81, 390).

Another possibility to mitigate radiation-induced damage of normal tissue is the intracellular stabilization of ROS scavenging enzyme levels, which are inactivated after irradiation due to a ROS burst and infiltration of neutrophils. Administration of DNA-sequences encoding ROS-scavenging enzymes ameliorate radiotherapy-induced cell damage (391). Ingestion of manganese

superoxide dismutase- plasmid liposomes (MnSOD-PL) has been shown to prolong mice survival after total body irradiation without protecting the tumor (392, 393). Mitochondrial localization of MnSOD-PL seems to be crucial for its efficient radioprotection (82). In order to further exploit anti-oxidant therapies, fusion peptides (nitroxides) with a high mitochondrial localization rate have been developed. JP4-039 stabilizes mitochondrial ROS scavenger levels reducing radiation induced anti-oxidant depletion and mitigating radiotherapy-induced damage in normal tissues (83, 84, 394), while a tumor-protective effect has been excluded (84, 395). Other studies have shown protective effects on normal tissues by recovery of stem cell function and differentiation (396, 397). Di-seleno-di-propionic acid (DSePA) is able to maintain the levels of ROS scavengers in irradiated mice, mitigates the ROS burst, reduces radiation-induced expression of pro-inflammatory cytokines, oxidative stress, pneumonitis and inflammation responses (85, 398). In mice oral administration is effective, contributing to potential improvement of patient compliance (85). The effects on normal tissue may be explained by the limited uptake of DSePA in tumors and the preferential accumulation in lung, intestine and kidney (86). Therefore, it is mainly investigated as co-therapy for cancer patients facing upper body radiotherapy.

Inflammation Mitigators

Other approaches aim to exploit the differential response of normal and cancer cells to stress (DSR) (**Figure 1**). These treatments amplify radiation-induced stress in tumor tissues whereas they ameliorate the normal tissue reaction. TNFα activation mediates the expression of NADPH-oxidases, promoting oxidative stress which damages healthy tissues and severely affects the patient's quality of life. Therefore, these molecular pathways are investigated as a potential treatment target.

Cyclooxygenase-2 (COX2), involved in the prostaglandin synthesis, is overexpressed in many cancers and is associated with chemoradioresistance. Radiotherapy further enhances its expression *via* NF-κB signaling pathways. Consequently, blocking of COX2 and NF-κB-signaling improves radiotherapy response (399). Elshawi et al. demonstrated in mice that COX2 inhibition with a benzopyran compound mitigated radiation-induced NF-κB and COX2 activity. The treatment also ameliorated other radiotherapy-induced effects such as the increase of cytokines and decrease of liver enzymes (400). Celecoxib, another COX2 inhibitor, reduces radiation-induced skin toxicity in mice (401), which has been confirmed by other studies, reporting that celecoxib treatment enhances radiosensitization and reduces tumor growth (399, 402, 403). The results of a phase 2 trial investigating the effects of celecoxib combined with radiochemotherapy in NSCLC patients however were inconclusive (404). A second study treating colorectal cancer patients with celecoxib and chemoradiation stated an ameliorating effect on skin toxicity compared to earlier studies (87).

Naturally occurring compounds such as ascorbic acid, curcumin, melatonin, caffeic acid phenol ester and vitamin E are associated with radioprotective effects on normal tissues whereas they stimulate the radiosensitivity of tumor tissues. High doses of vitamin E and ascorbic acid demonstrated radiosensitizing effects in multiple cancer types (88–91). Intravenous administered ascorbate increases the therapeutic ratio by increasing radiation-induced DNA damage in pancreatic tumors and simultaneously decreasing DNA lesions in a non-carcinogenic tissues (90). Furthermore, ascorbate is suggested to downregulate the expression of the ROS scavenger MnSOD in cancer cells by controlling the NF-κB component RelB, whereas it upregulates MnSOD expression in normal cells (91). In agreement, Alexander et al. reported that supplementation of ascorbate mitigates the decrease of ROS scavengers in normal tissue of mice (90). Furthermore, they state in phase 1 trials that ascorbate supplemented to radiochemotherapy for pancreatic cancer patients is safe and potentially enhances treatment efficacy (90).

Curcumin blocks NF-κB signaling by inhibiting IκBα dissociation and TNFα-dependent pathway activation (92). In agreement, Cho et al. described in rats that curcumin counteracts the IR-induced TNFα expression and NF-κB translocation to the nucleus, which eventually alleviates radiotherapy-induced pneumonitis (405). This is substantiated by a study stating that curcumin reduced IL4 and NADPH-oxidase levels post-IR, which was associated with lower pneumonitis levels (406).

Melatonin (MLT) ameliorates radiation-induced oxidative stress by depleting hydroxyl radicals directly and by stimulating the activity of GPx and SOD, whereas it reduces the activity of ROS producing enzymes (NOS, NOX2/4) in normal cells (93, 407–409). Additionally, MLT downregulates NF-κB-signaling, mitigating an inflammatory response and enhances expression of DNA-repair genes contributing to genomic stability in normal cells (410–412). However, evidence implies that MLT combined with metformin exerted both synergizing and antagonizing effects in healthy rodents in a tissue-specific manner (94, 413). Findings in xenografts suggested that MLT exerts tumor-sensitizing effects by reducing DNA repair and stimulating OXPHOS in malignant cells intensifying the oxidative stress. Simultaneously it reverses the Warburg effect by potentially inhibiting mitochondrial PDK (414–416). Clinical trials on MLT however reported heterogeneous results. Onseng et al. examined the effects of MLT supplementation to chemoradiotherapy of head and neck cancer patients reporting a delayed onset of grade 3 oral mucositis (95), however without differences in mucositis incidence and quality of life. Treating breast cancer patients with a MLT-emulsion resulted in a lower dermatitis incidence (96). Post-radiotherapy MLT treatment is proposed to mitigate long-term radiation effects (417). Others did not observe synergistic effects with radiotherapy, although only upon comparison with controls from other studies (97).

Caffeic acid phenyl ester (CAPE) may exert its radiosensitizing effect in cancer cells by suppression of NF-κB-signaling and is associated with decreased glutathione-reductase levels and increased glutathione-peroxidase levels. As a result of this redox-imbalance ROS levels are increased (418, 419). Moreover, it re-sensitizes radiation-resistant breast cancer cells

by impairing the DNA repair and thus, enhancing IR-induced genomic instability (420). In normal cells on the other hand, CAPE mitigates cellular oxidative stresses by enhancing ROS scavengers expression levels and by interference with radiation-induced NF-κB-signaling (98, 99). Also reduced expression of cytokines preventing fibrosis of lung tissue post-radiation has been observed (98).

Vitamin E and its derivates are proposed to cause a differential stress response between tumor and normal tissues (421). In combination with radiochemotherapy, vitamin E ameliorates treatment-induced mucositis in head and neck cancer patients (89). Especially, the vitamin E derivative γ-tocotrienol received attention as anti-cancer treatment having based on its superior antioxidant capacity. Kumar et al. reported that the lipid peroxidation levels in tumor tissue increases under γ-tocotrienol administration, whereas specific adjacent tissues are protected (88). Moreover, they observe a reduction in radiation-induced lipid peroxidation in a tissue-dependent manner. The relatively low bioavailability of tocotrienols may be enhanced by optimizing administration schedule (422).

DNA Repair/Genomic Maintenance

Radiation and ROS-induced DSBs activate ataxia telangiectasia mutated (ATM) signaling promoting p53-induced cell cycle arrest and epigenetic marking of DSBs to facilitate DNA repair plays a central role in the decision whether to promote survival or induce cell death to prevent tumorigenesis (423, 424). It is proposed that polyphenol resveratrol (RSV) provokes a differential stress response and radiosensitizes cancer cells *via* interference with ATM-signaling and apoptosis cascade. It inhibits the expression of Mcl-1 by downregulation of STAT3 signaling (100, 425). Vendrely et al. demonstrated that RSV combined with capsaicin and radiotherapy inhibits ATM-based DNA repair in pancreatic cancer cells and increases phosphorylated p53. Activation of p53 results in cell cycle arrest and promotes apoptosis by increasing the Bcl-2/Bax ratio (101). Several other studies substantiated this, reporting RSV-associated G_0/G_1 arrest (426), a cell cycle phase with higher radiosensitivity compared to S-phase cells (426, 427).

The tumor suppressor p53 is required for maintenance of a G_1 arrest and determines the cellular fate. Serine/threonine kinase (Akt) influences p53-mediated effects by decreasing its pro-apoptotic effects. Thus, high pAkt levels favor cellular survival whereas low pAkt levels favor apoptosis (428). Interestingly, RSV is associated with downregulation of E2F1 and its downstream target pAkt (429–431). Multiple studies on RSV and radiotherapy have demonstrated its radiosensitizing effects in several carcinoma cells and *in vivo* (101, 429, 432–434). On the other hand, RSV and 3,3′-diindolylmethane combination treatment prior to radiotherapy stabilizes the levels of radical scavenging enzymes, reduces genomic alterations such as micronuclei formation and mitigated radiation-induced normal tissue damage in mice (435–437). Moreover, it directly activates ATM signaling in a context of oxidative stress, which may explain the opposing effect in cancer and normal cells (438). However, its clinical use is limited by its metabolic instability, low bioavailability (439) and photosensitivity (440). More stable RSV analogues such as HS-1793 have been associated with an improved radiotherapy response in xenografts by modulating the anti-cancer immune response (102).

DIETARY INTERVENTIONS INFLUENCING THE RADIOTHERAPY RESPONSE

Not only drugs and compounds could be of benefit to improve the therapeutic window, also dietary interventions could contribute to a more favorable treatment outcome (**Figure 1**, **Table 2**). Malignant cells display different metabolic needs than normal cells, because of their uncontrolled proliferative potential and often impaired OXPHOS, which results in elevated ROS levels. Short-term fasting (STF) and ketogenic diet (KD) exploit the difference in tolerability of oxidative stress between cancers cells and normal tissues by reducing global plasma glucose levels and increasing ketone body levels (441–443). A minimum of 24 h fasting prior treatment sensitized xenografts to radio-/chemotherapy (103, 104, 444). KD had a similar effect in xenografts exposed to radiochemotherapy and prolonged the overall survival co-occurring with enhanced protein oxidation, indicating that high ketone and low glucose levels amplified the ROS-induced damage in malignant cells (445). Moreover, KD may intensify energetic stress in tumors which display TCA cycle mutations, since these tumors are not able to utilize acetyl-CoA derived from the β-oxidation. Furthermore, evidence points towards a higher production of the oncometabolite 2-HG concurrent to increased β-oxidation in $IDH1_{mut}$ glioblastoma cells (446).

Normal tissues react differently to glucose deprivation in presence of ketone bodies as they display a higher metabolic flexibility, reducing their proliferative potential to remain in G_0-phase. Furthermore, they circumvent an energy deficit relying on FA-oxidation and OXPHOS (442). Abdelwahab et al. argues that there is no correlation between plasma glucose levels and cellular survival *in vivo*, indicating that metabolic reprogramming itself does not exert significant anti-tumor effects (442). Using pancreatic cancer xenografts, they demonstrate that 24 h fasting prior to radiotherapy prolongs survival and protects small intestinal stem cells optimizing the regeneration of adjacent, damaged tissues without tumor protection (104) Furthermore, they argue that this effect may occur due to a reduced apoptosis rate in fasted animals, since fasted animals display significantly lower cleaved caspase-3 levels. The combination of cisplatin treatment and caloric restriction also provoked a DSR in xenografts (447). Shi et al. demonstrates that fasting led to AMPK and ATM/p53 signaling in both normal and cancer cells (447). However, normal cells display increased levels of phosphorylated p53 resulting in G_0/G_1 phase arrest and less vulnerability to cisplatin treatment. Cancer cells maintain normal levels of phosphorylated p53 and cell cycle progression enhancing their sensitivity against cisplatin-induced damage compared to unfasted controls (447). Despite these results, the authors conclude that the introduction of caloric reduction into clinics is not advisable since many cancer patients already suffer from cachexia (104, 448).

KD mirrors the molecular effects of fasting, but does not enhance the cachexic phenotype of patients in phase 1 trials (443, 449, 450). These studies suggest that the combination of KD and radiotherapy synergizes in xenografts, but large cohort studies are currently lacking. Furthermore, they report that patient diet compliance is difficult with a lot of drop-out in these clinical studies. In addition, it is until now unclear what the best KD administration starting point before treatment is. A different route of administration *via* PEG tubes may facilitate treatment compliance (449). Another possibility may be mimicking the molecular effects using different drugs, such as metformin (104, 451). Cuyàs et al. reports an increase of ketone bodies and α-KG in HER2-positive breast cancer patients treated with metformin and chemotherapy (451).

CONCLUSION AND PERSPECTIVES

Modulating cellular metabolism to increase anti-cancer therapy efficacy is a powerful strategy, evidenced by the clinical implementation of some of these modulators. However, the utility of most of these metabolism-modulating compounds is limited due to low bioavailability, adverse and off-target effects. Adverse effects may occur less or more depending on the delivery route as seen for amifostine. Therefore, it is crucial to identify for every compound the optimal conditions for administration. Often alternative administration methods mitigate adverse effects and slightly enhance the bioavailability. Hence, attempts are made to develop derivatives and analogues of these compounds which mirror the effect of their parent compound and potentially reducing the binding to off-targets and subsequently reduce adverse effects. The success of metabolic interventions depends on the metabolic pattern of the primary tumor, metastatic lesions and the tumor's micro-environment, which shows a large intra- and intercellular variability due to different nutritional requirements for proliferation/invasion and metastasis formation, and thus requires understanding and assessment of this pattern. Influencing the primary tumor's metabolism could potentially also increase EMT, thereby causing a higher invasiveness potential or a more radioresistant phenotype of the metastasis.

As the tumor and TME metabolism are very dynamic processes, interactions between substrate availability and different metabolic pathways are very complex. There are close relationships reported between e.g. glycolysis, PPP, glutamine metabolism, FAO, TCA cycle, and OXPHOS as often substrates, by-products, and end-products often interact with multiple metabolic and signaling pathways. Rewiring the tumor's metabolism is therefore very challenging. Combining rewiring metabolism with radiotherapy creates challenges and opportunities for successful implementation in clinical practice. Creating more therapeutic resistant tumors, increasing their metastatic potential, or induce adverse normal tissue effects needs to be prevented. Therefore, more research on this topic is needed to elucidate these risks.

Overall, the malignant, metabolic rewiring and its implications on treatment response is complex. However, first attempts exploiting this phenomenon demonstrate promising results to further optimize our current anti-cancer therapies and to improve the therapeutic window for patients.

AUTHOR CONTRIBUTIONS

Conceptualization of the review was performed by MG and LD. MG and EZ wrote the first draft. All authors revised and edited the manuscript. All authors contributed to the article and approved the submitted version.

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